(2)

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Synthesis of Ring Fluorinated Pyrazoles and Isoxazoles. The Effect of 2-Fluoro and 2-Chloro Substituents On The Keto-Enol Equilibria of 1,3-Diketones N/A

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DOD Personnel
NCSU Chemistry Faculty

To develop a synthesis of ring fluorinated heterocycles. A variety of pyrazoles and isoxazoles can now be prepared conveniently in one step, starting from their corresponding 2-fluoro-1,3-diketones, using EtOH as the solvent and an acid as the catalyst. The effect of fluorine and chlorine on the keto-enol equilibria of 1,3-diketones was also examined and rationalized on the basis of stereoelectronic effects.

fluoro-pyrazoles, fluoro-isoxazoles,
2-fluoro-1,3-diketones, Et(H),
Keto-enol equilibria

39

unclassified unclassified unclassified unlimited

SYNTHESIS OF RING FLUORINATED PYRAZOLES AND ISOXAZOLES. THE EFFECT OF 2-FLUORO AND 2-CHLORO SUBSTITUENTS ON THE KETO-ENOL EQUILIBRIA OF 1,3-DIKETONES

by

JOSEPH C. SLOOP

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APPROVED BY:

Robert C. Sloop Suzanne T. Purrington

Carl L Bumgardner
Chair of Advisory Committee

ABSTRACT

SLOOP, JOSEPH C. Synthesis of Ring Fluorinated Pyrazoles and Isoxazoles. The Effect of 2-Fluoro and 2-Chloro Substituents on the Keto-Enol Equilibria of 1,3-Diketones. (Under the direction of Dr. Carl L. Bumgardner.)

The purpose of this work was to develop a synthesis of ring fluorinated pyrazoles and isoxazoles. A variety of the compounds can now be prepared conveniently in one step, starting from their corresponding 2-fluoro-1,3-diketones, using EtOH as the solvent and an acid as the catalyst. The effect of fluorine and chlorine on the keto-enol equilibria of 1,3-diketones was also examined and rationalized on the basis of stereoelectronic effects.

DEDICATION

To my Family - whose continued faith and support made this endeavor possible.

BIOGRAPHY

The author [redacted]-olina. He received his high school education at A. L. Brown High School in Kannapolis, North Carolina. He then attended Davidson College in Davidson, North Carolina where he received his Bachelor of Science degree in Chemistry in 1983.

In the spring of 1983, the author was commissioned an officer in the United States Army where he currently serves on active duty in the Chemical Corps. The author initiated graduate studies in the Department of Chemistry at North Carolina State University at Raleigh in the Fall of 1988. He is a member of the Phi Lambda Upsilon chemistry honor fraternity, and the Phi Kappa Phi honor fraternity.

ACKNOWLEDGEMENTS

The author expresses his deep appreciation to the many people who contributed to this study. Sincere appreciation is expressed to Dr. C. L. Bumgardner, chairman of the Advisory Committee, for providing guidance and inspiration during the course of this research.

Appreciation is also extended to Dr. S. T. Purrington whose advice directly contributed to the success of this project. The author is also grateful to Mr. Michael Shockley and Mr. Jason Burgess for their time in running ^{1}H, ^{19}F, ^{13}C NMR spectra and for their advice in spectral interpretation. Gratitude is also afforded Mrs. Carol Haney for the running of Mass Spectra in support of this work.

Fondest gratitude is expressed to his wife, Linda, and children, Lori and Joey, for their patience, understanding, love and support.

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INTRODUCTION

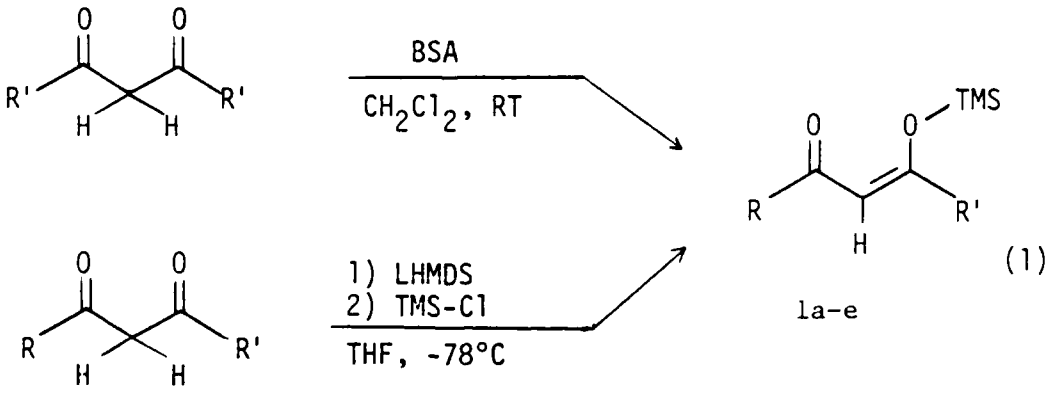
An increasing number of agrochemicals and pharmaceuticals contain fluorine atoms.[1] The presence of F drastically alters the electronic nature of a compound without changing its size significantly. Fluorine withdraws electrons via the σ-bond yet can donate elect by way of π-systems. In addition, the high C-F bond strength results in fluorine acting as a poor leaving group. This combination of properties makes fluorine-containing compounds useful and sometimes unique. The need for new routes for introducing F selectively into a variety of substrates therefore continues to grow. Among the fluorine containing compounds, in particular, pyrazoles and isoxazoles fluorinated on the heterocyclic ring represent a class essentially unexplored.

Since 2-fluoro-1,3-diketones have recently become available[3] and since 1,3-diketones have been used for years as starting materials for heterocyclic syntheses,[4-6] we examined the possibility of employing these new fluorinated diketones as building blocks for synthesizing fluoro-pyrazoles and isoxazoles.

In addition, preparation of new 2-fluoro-1,3-diketones enabled us to study in more detail the remarkable effect of fluorine[3,7] on the keto-enol equilibria of 1,3-diketones.

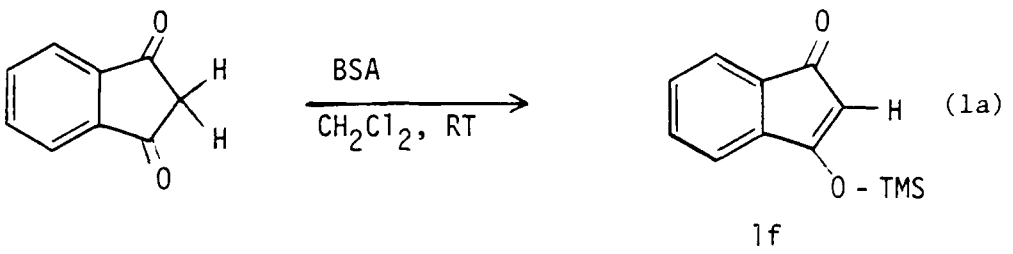
RESULTS

The desired 2-fluoro-1,3-diketones were prepared from silyl enol ethers and dilute fluorine.[3] The series was chosen so as to have a variety of 1,3 substituents, including 1,3-diaryl, 1,3-dialkyl, 1-alkyl-3-aryl, and 1-trifluoromethyl-3-aryl moieties. A cyclic case, 2-fluoro-1,3-indanedione, was also prepared to provide another type structure for probing the effect of fluorine on the keto-enol equilibrium.[3] Table 1 summarizes the data on silyl enol ethers prepared by the scheme in equations 1 and 1a. In some cases, bis(trimethylsilyl)-acetamide (BSA) was used as the reagent, in others, lithium hexamethyldisilazide (LHMDS) followed by trimethylsilyl chloride (TMS-Cl) was used to prepare the silyl enol ethers. The reagents in equation 1 were found to be an improvement over hexamethyldisilazane[3] as the silylating agent.



(1)

a: R=R'=Ph; b: R=CH_3, R'=pNO_2Ph; c: R=R'=Me; d: R=Ph, R'=CF_3; e: R=R'=ptBuPh.



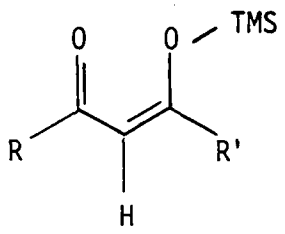
(1a)

1f

Table 1. Silyl Enol Ether Products (1)

	% Yield	
Compound	w/BSA	w/LHMDS
1a	90	60
1b	79	55
1c	81	62
1d	80	70
1e	84	60
1f	76	n/a

Since these silyl compounds are highly susceptible to hydrolysis, they were fluorinated immediately following their preparation. Fluorination was accomplished using 5% fluorine in nitrogen at -78°C as shown in equation 2 and 2a. The results are collected in Table 2.

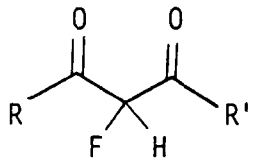


1

1a-e

5% F_2 in N_2

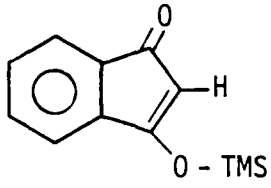
-78°C, Freon-11
various times



2

2a-d, e* (see Table 2)

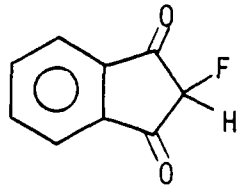
(2)



1f

5% F_2 in N_2

-78°C, Freon-11
1.5 h



2f

(2a)

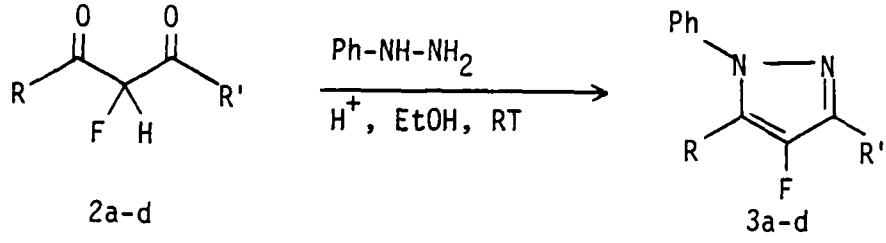
Table 2. Fluorination Products

Cmpd	% Yield	NMR Data ^1H[b]	NMR Data ^{19}F	Molecular Ion
2a	74	6.37 (d,1H,J_{HF}=51 Hz)	-187 (d,J_{FH}=51 Hz)	242
2b	84	5.5 (d,1H,J_{HF}=51 Hz)	-190 (d,J_{FH}=51 Hz)	225
2c	62	5.8 (d,1H,J_{HF}=51 Hz)	-190 (d,J_{FH}=51 Hz)	118
2d	60	5.8 (d,1H,J_{HF}=50 Hz)	-196 (d,J_{FH}=50 Hz); -81(s)	234
2e	15[a]		-105(s)	
2f	80	5.4 (d,1H,J_{HF}=51 Hz)	-207 (d,J_{FH}=51 Hz)	164

[a]Only difluoro product was obtained.

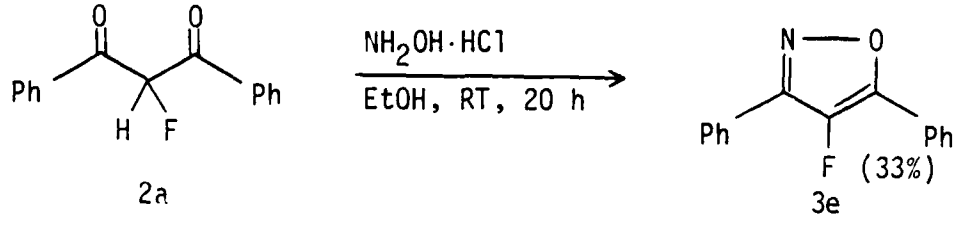
[b]Only signals for geminal proton-fluorine splitting are given. See experimental section for remaining NMR data.

Having a number of monofluorinated diketones via the route in equation 2, we then studied their reactions with phenylhydrazine under standard experimental conditions[4,6] for forming pyrazoles from 1,3-diketones (equation 3). Table 3 indicates the yields and data used to characterize the pyrazole products.



2a-d 3a-d (3)

Reaction of compound 2a with hydroxylamine hydrochloride in ethanol was also examined and gave isoxazole 3e in 33% yield, which was not optimized (equation 4). Compound 3e showed a singlet in the ^{19}F NMR at -173 ppm; multiplets in the ^{1}H NMR spectrum at 7.0-7.5 and 8.0-8.1, and a high resolution mass spectrum consistent with the structure given in equation 4.



2a 3e

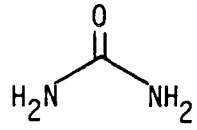
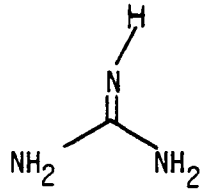
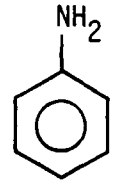
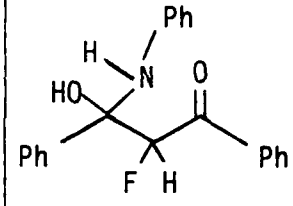
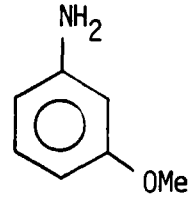
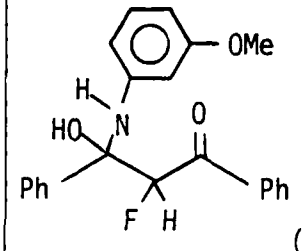
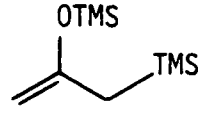
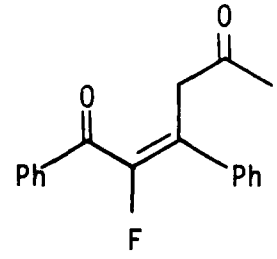
Cyclizations were attempted in EtOH at room temperature with several other bifunctional nucleophiles and diketone 2a. No cyclizations were achieved, but the products suggested by MS and NMR are listed in Table 4.

Table 3. Pyrazole Formation

Compound	% Yield	NMR (ppm)		MS (m/e)	
		^{19}F	^{1}H	Calcd	Found
3a[a]	83	-173s	7.2-7.5(m,10H); 8.0-8.2(m,5H)	--	314
3b	79	-175s	2.4(s,3H); 7.2-7.5(m,5H); 7.6-8.2(m,4H)	297.091350	297.091502
3c	85	-178s	2.25(s,3H); 2.35(s,3H); 7.2-7.7(m,5H)	190.090615	190.090646
3d	72	-173s	6.8-8.0(m,10H)	306.077990	306.078043

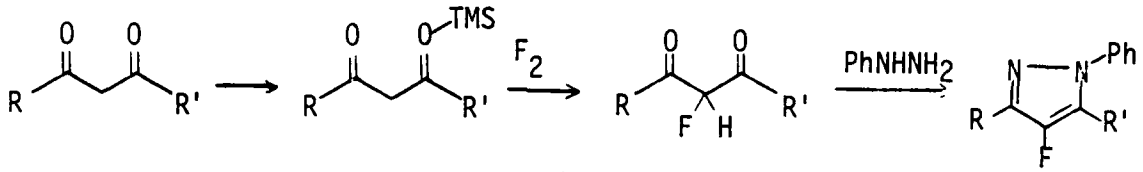
a. Combustion analysis obtained.

Table 4. Attempted Cyclizations of Compound 2a

Nucleophile	Product	% Yield
 (4)	none observed	
 (5)	none observed	
 (6)	 (3f)	52 (G.C.)
 (7)	 (3g)	58 (G.C.)
 (8)	 (3h)	27

DISCUSSION

Results described in Tables 1-3 clearly demonstrate that the sequence in Scheme 1 constitutes a practical route to a variety of ring-fluorinated pyrazoles, previously unavailable.



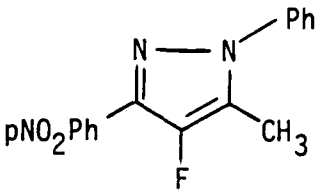
Scheme 1

Reactions of phenylhydrazine with compound 3d can give rise to two regioisomers as shown in Figure 1. Observation of $Ph-C\equiv\overset{+}{N}-Ph$

1 2

Figure 1

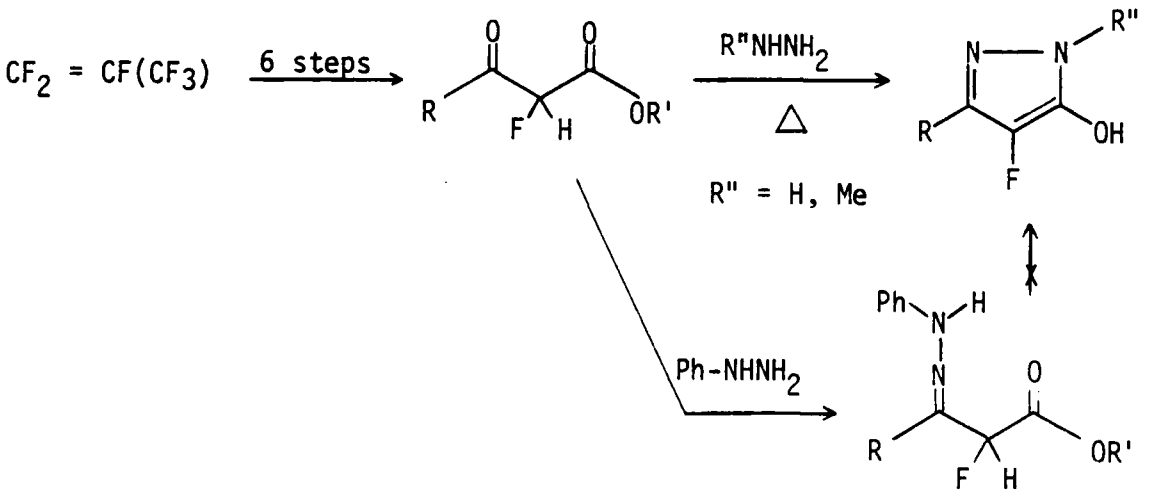
in the mass spectrum of compoud 3d indicates that regioisomer 2 was the product obtained. This regiochemistry was expected since the more nucleophilic ß-nitrogen of phenylhydrazine attacks the more electrophilic carbonyl (adjacent to the trifluoromethyl group). Analogously, compound 3b was assigned the regiochemistry shown in Figure 2. Formation of 3d indicates that the method in Scheme 1 can lead to previously unavailable pyrazoles which are both fluorinated and trifluoromethylated.[8]



3b

Figure 2

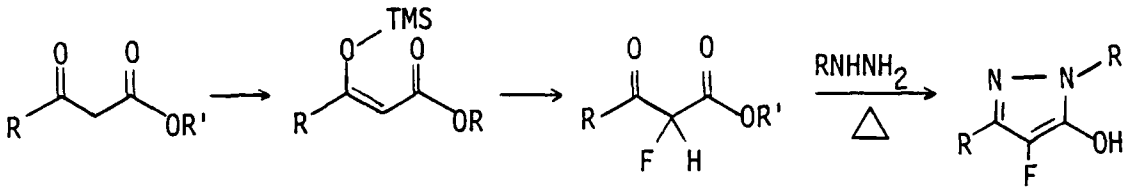
Interestingly, in an earlier study, hydroxypyrazoles were obtained by Ishikawa from 2-fluoro-1,3-ketoesters and hydrazines, but the synthetic scope of this reaction is limited to hydrazine and methylhydrazine. Attempted cyclizations with phenylhydrazine failed,[2] probably due to the decreased reactivity of the ester moiety, Scheme 2. The diketones used in this study do not suffer from this disadvantage. In addition, Ishikawa's route to the intermediate



Scheme 2

2-fluoro-1,3-ketoesters involved starting with perfluoropropene or trifluoroethene, resulting in a lengthy scheme which is inefficient with

respect to the use of fluorine. Since fluoro ketoesters, the Ishikawa precursors to fluoro-hydroxypyrazoles, can be prepared readily,[3] a more practical, economical synthesis of hydroxypyrazoles can now be delineated, as shown in Scheme 3.



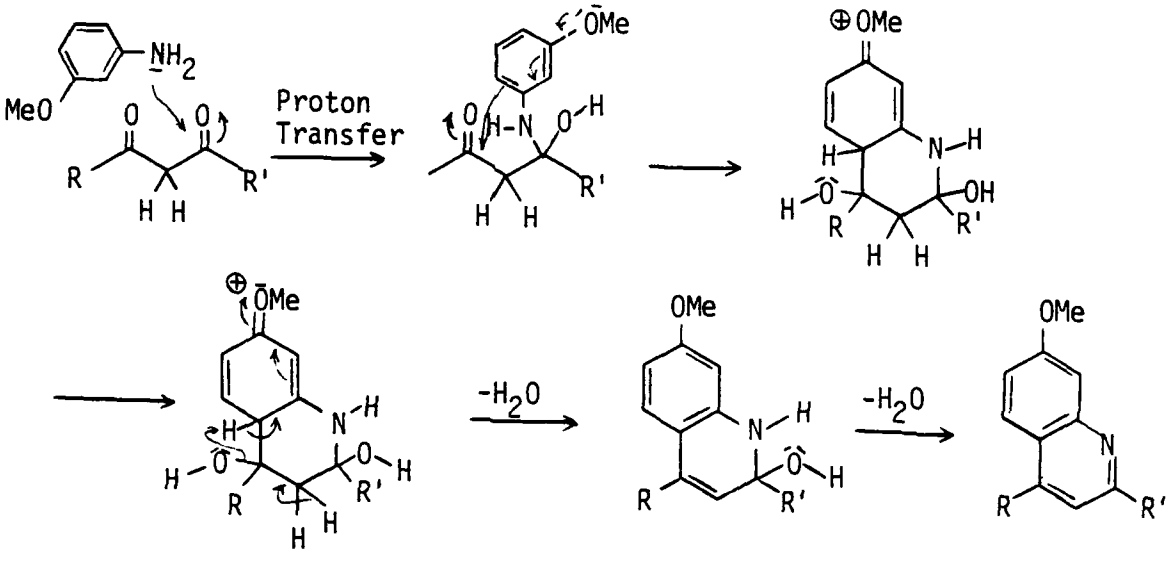
Scheme 3

Preliminary results (eq 4) also indicate that ring-fluorinated isoxazoles can be prepared readily. Although the yield was not high, no effort was made to optimize the results. Ring fluorinated isoxazoles have not been previously reported although several groups have mentioned trifluoromethylated derivatives.[8,9]

In order to examine the scope of the cyclization reactions of 2-fluoro-1,3-diketones further, we attempted to cyclize compound 2a with the nucleophiles listed in Table 4 where there are a wide range of reactivities. As shown neither urea (4) nor guanidine (5) proved to be acceptable nucleophiles for cyclization, even after refluxing for 12h in ethanol. This is not surprising since neither the carbonyl of urea nor the imine of guanidine is particularly nucleophilic. Both acid and base promoted condensations were attempted without success.

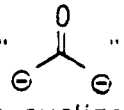
An effort to cyclize diketone 2a with nucleophiles 6 and 7 (Combes'Quinoline Synthesis)[5] gave only monoadducts. Combes originally noted that cyclizations of diketones with nucleophiles such

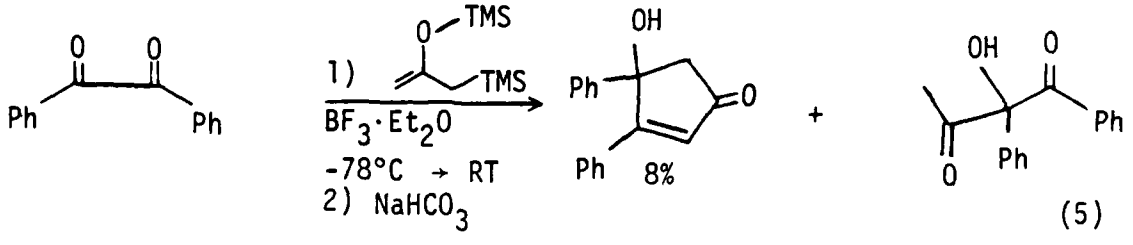
originally noted that cyclizations of diketones with nucleophiles such as aniline required extremely harsh conditions and in some cases led to decomposition. m-Anisidine enhanced the nucleophilicity of the aromatic ring and aided cyclization as shown in Scheme 4.



Scheme 4

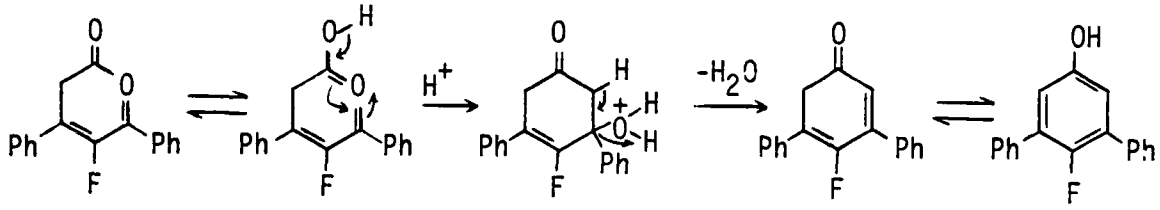
Even when the 2-fluoro-1,3-diketone and 7 were refluxed for 4h in acetic acid and HCl, no cyclization was noted.

Finally, cyclization with a dianion equivalent "  " was tested. Hosomi reported that 1,2-diketones could be cyclized with (2-siloxyallyl)-silanes, (8) in low yields. The major product was, however, a monoadduct, equation 5.[10]



(5)

We, likewise obtained the monoadduct shown in Table 4; there was no evidence of a cyclized product under our conditions. This reaction does, though, provide an intermediate that may undergo intramolecular aldol condensations to give fluoro-phenols, Scheme 5.



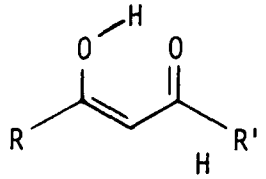
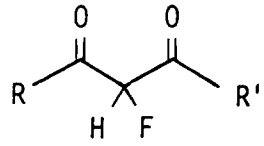
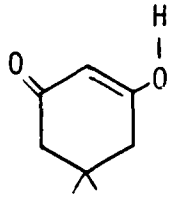
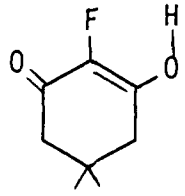
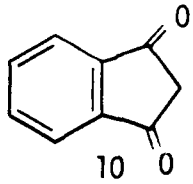
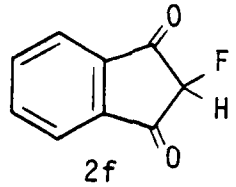
Scheme 5

Having prepared a variety of fluoro-diketones (Table 2), we examined the keto-enol equilibria. The NMR data collected in Table 2 clearly show that the 2-fluoro-1,3-diketones prepared in this study exist in the diketo form. All compounds clearly show doublets (J_{FH} ~ 50-52 Hz) in the ^{19}F NMR spectra between -187 ppm and -210 ppm, indicative of 2-fluoro substituted 1,3-diketones. The ^{1}H NMR spectra show doublets (J_{HF} ~ 50-52 Hz) between 5.5 ppm and 6.3 ppm, but no enolic proton signal at 11-13 ppm. In addition, there was no evidence of hydroxyl groups in the IR spectra of these compounds. This pattern agrees with results reported earlier regarding acyclic compounds but contrasts with the cyclic fluoro-dimedone (9) where the enol is the preferred isomer.

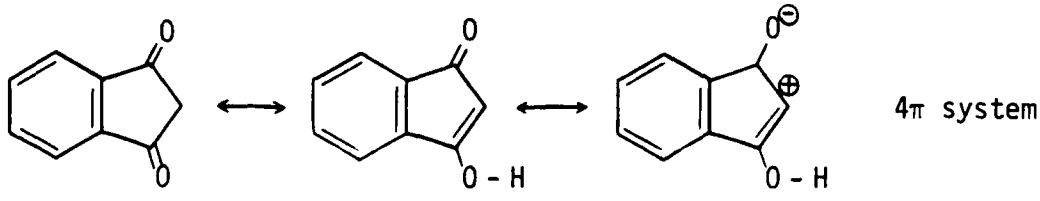
In order to examine more fully this apparent trend in cyclic 2-fluoro-1,3-diketones, we synthesized 2-fluoro-1,3-indanedione (2f). This compound, however, exists in the diketo form as does the parent 1,3-indanedione (10). Compound 2f clearly shows a doublet in the ^{19}F NMR at -207 ppm (J_{FH} = 51 Hz), and a doublet in the ^{1}H NMR at 5.4

ppm (J_{HF} = 51 Hz). The relations are summarized in Table 5 where comparisons in keto-enol equilibria are made between the parent 1,3-diketone and the fluorinated derivatives. Entries A and B were

Table 5. Comparison of Keto-Enol Equilibrium

Entry	Parent 1,3-diketone	2-Fluoro-1,3-diketone
A		
B		 9
C	 10	 2f

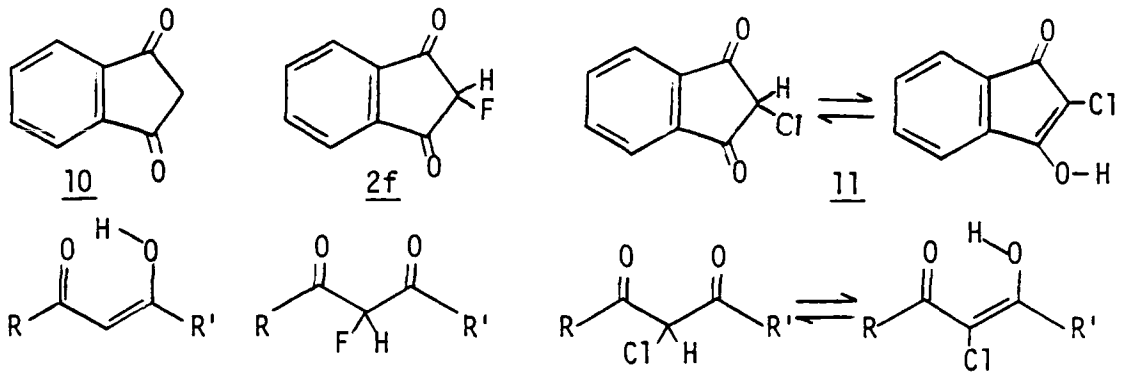
previously explained in terms of primary and secondary orbital interactions.[3] The enol forms of both 2f and 10 (entry C) are special in that they have antiaromatic character,[11] Scheme 6. This effect would destabilize the enol form and force the equilibrium to the diketo form in both the parent and fluorinated derivatives. An adverse strain effect could also be a factor since the enol form would require all 5 atoms in the 5-membered ring to be sp^2.



Scheme 6

Another important difference emerges when compound 2f is compared with 2-chloro-1,3-indanedione (11) (see Table 6).

Table 6. Comparison of 2-Fluoro and 2-Chloro 1,3-Diketones



In ethanol, whereas compound 2f has 0% enol character, compound 11 is 20% enolic.[12] Acyclic 2-fluoro-1,3-diketones, as we have shown, are 100% diketo, while the monochlorinated analogs are enolic. This apparent difference between fluorine and chlorine can be explained by noting their positions on the periodic chart. Fluorine, a 1st row element, has no d-orbitals and therefore cannot stabilize the enol form of 1,3-diketones by providing a LUMO with which the enol HOMO can interact. Chlorine, a 2nd row element, has empty d-orbitals available, so stabilization of the enol form of 1,3-diketones is now possible,[13] as shown in Figure 3.

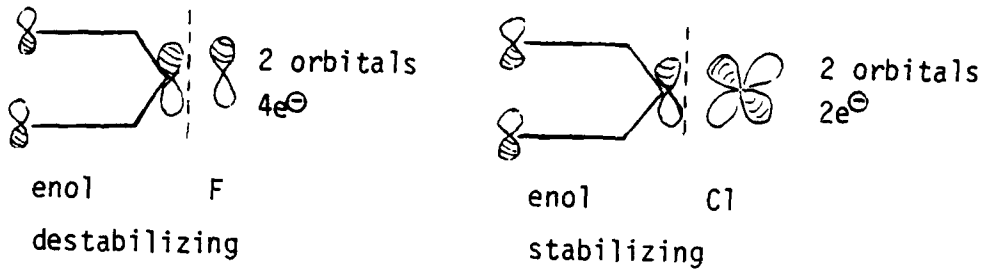


Figure 3

This d-orbital stabilization is also apparent in the acidity of $HCCl_3$ (12) and HCF_3 (13). It is known that 12 is a stronger acid than 13. The fluorines are believed to destabilize the deprotonated form of 13, $^-CF_3$, whereas the chlorines are believed to stabilize the conjugate base of 12, $^-CCl_3$.

In general then, we postulate that the presence of fluorine in the 2 position of a 1,3-diketone discourages enol formation, while the presence of chlorine encourages enol formation.

In any event, 2-fluoro-1,3-diketones can be used with phenylhydrazine and hydroxylamine to produce selectively fluorinated pyrazoles and isoxazoles in a practical manner. If trifluoromethyl groups are incorporated into the 2-fluoro-1,3-diketones, then fluorinated, trifluoromethylated products can be obtained as well.

EXPERIMENTAL

Melting points were determined on a Meltemp melting point apparatus and are uncorrected. The IR spectra were obtained from a Perkin-Elmer 1430 spectrometer. The ^{19}F NMR (84.67 MHz) were obtained on a Varian FM-390 NMR spectrometer. The ^{1}H and ^{13}C NMR spectra were obtained from a General Electric 300 MHz NMR spectrometer. Chemical shifts were reported in ppm relative to internal TMS for ^{1}H NMR data, internal $CDCl_3$ for ^{13}C NMR data, and external $CFCl_3$ for ^{19}F NMR data. $CDCl_3$ was the solvent used in all cases.

Gas chromatography (GC) was performed using a Hewlett-Packard 5890 gas chromatograph with a fused silica capillary column and used helium as a carrier gas. Thin layer chromatography (TLC) was done on Baker Flex silica gel IB-F coated plates. Visualization was accomplished with 254 nm (UV) light. All column chromatography was performed with Aldrich 70-270 mesh silica gel using a hexane/ethyl acetate mixture as the eluent system.

A Hewlett-Packard 5985 GC/MS spectrometer system was used to collect MS data and a JEOL HX1110 HF spectrometer was used to verify molecular weights of synthesized compounds. Analyses were performed by Atlantic Microlab, Inc.

STARTING MATERIALS

The following chemicals were available from Aldrich Chemical Company: dibenzoylmethane, bis(trimethylsilyl)acetamide (BSA), n-butyllithium, hexamethyldisilazane, boron trifluoride etherate, trimethylsilyl chloride, 2,4-pentanedione and 4,4,4-trifluoro-1-phenyl-1,3-butanedione. 1-(4-Nitrophenyl)-1,3-butandione was provided by Dr. S. T. Purrington. Fluorine, 5% diluted in nitrogen was obtained from Air Products and Chemical Company. Sodium fluoride (used as a scrubber) and potassium iodide (used in fluorination traps to destroy excess fluorine) were obtained from Fisher Scientific Company. Freon-11 was purchased from the Flura Chemical Company.

All solvents were dried and distilled prior to use: dichloromethane (CH_2Cl_2) from P_2O_5 under N_2, tetrahydrofuran (THF) from sodium benzophenone ketyl under N_2. Hexamethyldisilazane and trimethyl silyl chloride were purified by redistillation from calcium hydride.

GENERAL PROCEDURES FOR PREPARATION OF TRIMETHYLSILYL ENOL ETHERS OF 1,3-DIKETONES

In a flame dried 200 mL round bottom flask, equipped with a magnetic stirring bar and connected to a nitrogen bubbler are placed 20 mL dry dichloromethane and 9 mmol of the diketone. The solution is stirred while 10 mmol of BSA was added to the solution dropwise. After stirring at room temperature various times, the excess BSA and by-products were removed by rotary evaporation.

1,3-Diphenyl-3-[(trimethylsilyl)oxy]-2-propen-1-one (1a)

To 2.00 g (0.0090 mol) dibenzoylmethane in 25 mL of dichloromethane at 0°C was added dropwise 2.24 mL (0.00908 mol) BSA. The mixture was allowed to warm to room temperature and stirred for 18 h. The solvent was removed by evaporation. 2.42 g (90%) of a yellowish liquid was obtained. ^{1}H NMR (δ): 0.01-0.02 (s, 9H), 6.75-6.8 (s, 1H), 7.1-7.85 (m, 10H).

1-(4-Nitrophenyl)-1-[(trimethylsilyl)oxy]-1-buten-3-one (1b)

To 0.290 g (0.00145 mol) 1-(4-nitrophenyl)-1,3-butanedione in 20 mL dichloromethane was added 0.360 mL (0.00145 mol) BSA dropwise. The mixture was stirred for 68 h and the solvent was removed by evaporation. 0.320 g (79%) of a yellowish liquid was obtained (b.p. 130°C/10 mm Hg) that hydrolyzed rapidly.

4-[(Trimethylsilyl)oxy]-3-penten-2-one (1c)

To 1.20 g (0.0120 mol) 2,4-pentanedione in 40 mL dichloromethane was added 2.97 mL (0.0120 mol) BSA dropwise. The mixture was stirred for 48 h and the solvent was removed by evaporation. 1.61 g (81%) of a yellowish liquid was obtained by fractional distillation, (b.p. 52-54°C/10 mm Hg), lit.[3] 54°/10 mm Hg.

1-Phenyl-4,4,4-trifluoro-3-[(trimethylsilyl)oxy]-2-buten-1-one (1d)

To 1.20 g (0.00560 mol) 1-phenyl-4,4,4-trifluoro-1,3-butanedione in 20 mL dichloromethane was added 1.37 mL (0.00560 mol) BSA dropwise. The mixture was stirred for 40 h and the solvent removed by evaporation. 1.30 g (80%) of a yellowish oil was obtained (b.p. 105°/10 mm Hg) that hydrolyzed rapidly.

1,3-Di-(4-tertbutylphenyl)-3-[(trimethylsilyl)oxy]-2-propen-1-one (1e)

To 1.20 g (0.00350 mol) of di-p-tertbutylbenzoylmethane in 20 mL dichloromethane was added 0.870 mL (0.0035 mol) of BSA dropwise. The mixture was stirred for 70 h and the solvent was removed by evaporation. 1.20 g (84%) of a yellowish oil was obtained that hydrolyzed upon attempted distillation.

3-[(Trimethylsilyl)oxy]-2-inden-1-one (1f)

To 1.00 g (0.00680 mol) 1,3-indanedione in 20 mL of dichloromethane at 0°C was added dropwise 1.70 mL (0.00610 mol) BSA. The mixture was allowed to warm to room temperature and stirred for

24 h. The solvent was removed by evaporation. 1.13 g (76%) of a reddish liquid was obtained which hydrolyzed upon attempted distillation.

ALTERNATIVE PROCEDURE FOR PREPARATION OF COMPOUNDS 1a-e

Compounds 1a-e were also prepared in an analogous fashion using hexamethyldisilazide as the base. All molar ratios of reactants are the same as are the solvent volumes.

GENERAL FLUORINATION PROCEDURE

The reactant was placed in a 20 cm bubbler tube reactor made of ordinary glass and then diluted with 20-25 mL $CFCl_3$. The mixture was stirred and cooled to a constant -78°C under N_2. Five percent fluorine in N_2 was then bubbled through the bubbler tube for a specified period of time (see Figure 4). After the reaction, nitrogen was bubbled through for 10 min to flush unreacted fluorine through the exit traps. The solvent was removed by rotary evaporation and the crude products purified by chromatography.

FLUORINATION SET-UP

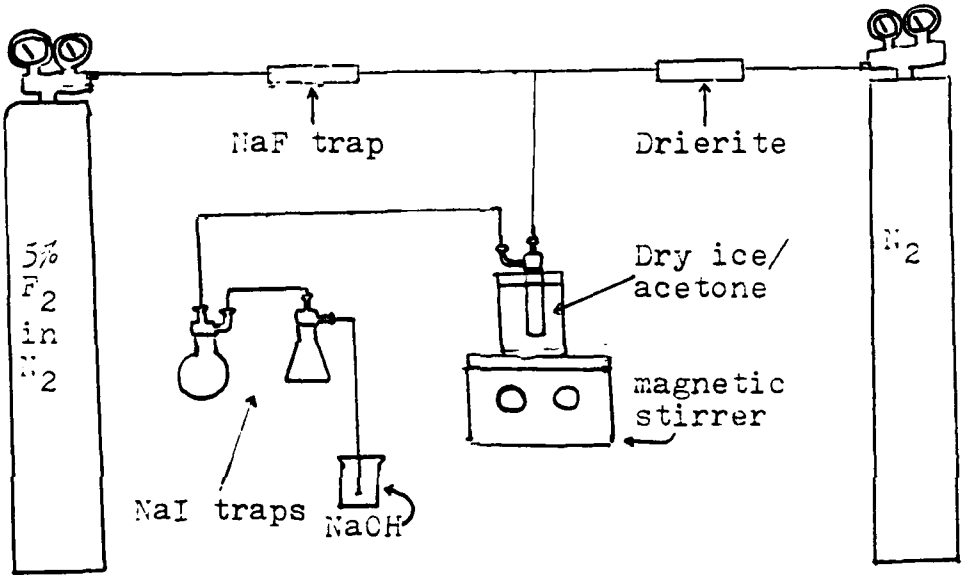


Figure 4

2-Fluoro-1,3-diphenyl-1,3-proponedione (2a)

To 2.40 g (0.00816 mol) of compound 1a in 20 mL of Freon-11 at -78°C was added 5% fluorine in nitrogen for 2 h. The crude product was purified by chromatography and recrystallized from hexanes. 1.46 g (74%) of light-yellowish crystals were obtained, m.p. 74-75°C, lit.[3] 72-74°C. ^{1}H NMR (δ): 6.37 (d, 1H, J_{HF} = 51.9 Hz), 7.4-7.6 (m, 5H), 8.1-8.2 (m, 5H). ^{19}F NMR (ppm): -187 (d, J_{FH} = 51.9 Hz). IR (CCl_4) (cm^{-1}): 3060 (C=C-H), 1680-1705 (C=O), 1200 (C-F). Mass spectral data (m/e): 242.

2-Fluoro-1-(4-nitrophenyl)-1,3-butanedione (2b)

To 0.300 g (0.00110 mol) of compound 1b in 20 mL of Freon-11 at -78°C was added 5% fluorine in nitrogen for 1.25 h. The crude product was purified by recrystallization from hexanes. 0.210 g (84%) of yellowish, brown crystals were obtained, m.p. 103-104°C. ^{1}H NMR (δ): 2.40 (s, 3H), 5.5 (d, 1H, J_{HF} = 51.5 Hz), 6.8-7.6 (m, 2H), 8.1-8.4 (m, 2H). ^{19}F NMR (ppm): -190 (d, J_{FH} = 51.5 Hz). IR (CCl_4) (cm^{-1}): 3025 (C=C-H), 1525 (C=O), 1210 (C-F). Mass spectral data (m/e): 225.

3-Fluoro-2,4-pentanedione (2c)

To 1.20 g (0.00720 mol) of compound 1c in 20 mL of Freon-11 at -78°C was added 5% fluorine in nitrogen for 2.1 h. The crude product was purified by fractional distillation. 0.500 g (62%) of a pale yellow liquid was obtained, b.p. 129.5-132°C. ^{1}H NMR (δ): 2.0-2.1 (s, 6H), 5.8 (d, 1H, J_{HF} = 51.3 Hz). ^{19}F NMR (ppm): -190 (d, J_{FH} = 51.2

Hz). IR (neat) (cm^{-1}): 1670-1695 (C=O), 1120 (C-F). Mass spectra data (m/e): 118.

2,4,4,4-Tetrafluoro-1-phenyl-1,3-butanedione (2d)

To 1.20 g (0.00420 mol) of compound 1d in 20 mL of Freon-11 at -78°C was added 5% fluorine in nitrogen for 2.0 h. The crude products were purified by chromatography. 0.600 g (60%) of off-white crystals were obtained, m.p. 72-74°C. ^1H NMR (δ): 5.8 (d, 1H, J_{HF} = 50.2 Hz), 7.4-7.5 (m, 2H), 7.6 (m, 1H), 7.9-8.1 (m, 2H). ^{19}F NMR (ppm): -196 (d, J_{FH} = 50.3 Hz), -81 (s). IR (CCl_4) (cm^{-1}): 3020-3080 (C=C-H), 1670-1710 (C=O), 1205-1100 (C-F). Mass spectral data (m/e): 234.

2,2-Difluoro-1,3-di-(4-tertbutylphenyl)-1,3-propanedione (2e)

To 1.20 g (0.00290 mol) of compound 1e in 20 mL of Freon-11 at -78°C was added 5% fluorine in nitrogen for 2.75 h. 0.170 g (15%) yellowish liquid was obtained which upon attempted purification by column chromatography converted 2e to non-fluorinated 1,3-diketone. ^1H NMR (δ): 1.2 (s, 9H), 1.3 (s, 9H), 7.2-8.0 (m, 8H). ^{19}F NMR (ppm): -105 (s).

2-Fluoro-1,3-indanedione (2f)

To 1.00 g (0.00461 mol) of compound 1f in 20 mL of Freon-11 at -78°C was added 5% fluorine in nitrogen for 1.5 h. The crude product was purified by chromatography and recrystallized from hexanes. 0.610 g (80%) of a yellow solid was obtained, m.p. 94-96°C. ^1H NMR (δ): 5.4 (d, 1H, J_{HF} = 51.0 Hz), 7.6-8.2 (m, 4H). ^{19}F NMR (ppm): -207

(d, J_{FH} = 51.1 Hz). IR (CH_2Cl_2) (cm^{-1}): 3075 (C=C-H), 1605 (C=O), 1210 (C-F). Mass spectral data; (m/e) calcd: 164.02740; Found: 164.027580.

GENERAL CYCLIZATION SYNTHETIC SCHEME

To 4 mmol of the diketone in 10 mL absolute EtOH is added ~5 mmol of nucleophile. After 5-10 min, concentrated acid is added (in varying quantities and types) slowly to prevent the reaction mixture temperature from rising too rapidly. The reaction is allowed to proceed at room temperature for various times. The crude products are purified by chromatography or recrystallized from hexanes and/or ether.

3-Fluoro-1,2,4-triphenylpyrazole (3a)

To 1.20 g (0.00490 mol) of compound 2a in 10 mL absolute ethanol is added 0.526 mL (0.00540 mol) phenyl hydrazine. After 10 min, 2 mL of concentrated sulfuric acid was added dropwise and stirred at room temperature for 16 h. The crude product was purified by recrystallization from hexanes, 1.057 g (83%) of yellowish-brown crystals were obtained, m.p. 141-142°C. ^{1}H NMR (δ): 7.2-7.5 (m, 10H), 8.0-8.2 (m, 5H). ^{19}F NMR (ppm): -177 (s). IR (CCl_4) (cm^{-1}): 3060 (C=C-H), 1600-1640 (C=N), 1200 (C-F). Mass spectral data (m/e): 314. Anal.: calcd for $C_{21}H_{15}FN_2$, C: 80.25%, H: 4.78%, N: 8.92%. Found: C: 80.17%, H: 4.85%, N: 8.90%.

3-Fluoro-4-methyl-2-(4-nitrophenyl)-5-phenylpyrazole (3b)

To 0.190 g (0.000850 mol) of compound 2b in 10 mL absolute ethanol was added 0.0800 mL (0.00085 mol) phenylhydrazine. After 10 min, 1 mL of concentrated sulfuric acid was added dropwise and stirred at room temperature from 44 h. 0.201 g (79%) of a yellowish-brown solid was obtained, decomposing at 240°C. ^{1}H NMR (δ): 2.4 (s, 3H), 7.2-7.5 (m, 5H), 7.6-8.2 (m, 4H). ^{19}F NMR (ppm): -175 (s). IR (CH_2Cl_2) (cm^{-1}): 3050 (C=C-H), 1700 (C=N), 1215 (C-F). Mass spectral data; (m/e) calcd: 297.091350; found: 297.091502.

3-Fluoro-2,4-dimethyl-1-phenylpyrazole (3c)

To 0.600 g (0.00560 mol) of compound 2c in 10 mL absolute ethanol was added 0.530 mL (0.00570 mol) phenylhydrazine. After 10 min, 1 mL of concentrated sulfuric acid was added dropwise and

stirred at room temperature for 36 h. 0.900 g (85%) of a reddish liquid was obtained upon fractional distillation, b.p. 98-100°C/10 mm Hg. ^{1}H NMR (δ): 2.25 (s, 3H), 2.35 (s, 3H), 7.2-7.7 (m, 5H). ^{19}F NMR (ppm): -178 (s). IR (CH_2Cl_2) (cm^{-1}): 3070 (C=C-H), 1650-1710 (C=N), 1215 (C-F). Mass spectral data; (m/e) calcd: 190.090615; found: 190.090646.

3-Fluoro-4-trifluoromethyl-1,2-diphenylpyrazole (3d)

To 0.580 g (0.00250 mol) of compound 2d in 10 mL absolute ethanol was added 0.243 mL (0.00250 mol) phenylhydrazine and 1 mL concentrated sulfuric acid and stirred for 70 h, then refluxed for 2 h. 0.550 g (72%) of a yellowish-brown solid was obtained, 263° dec. ^{1}H NMR (δ): 6.8-8.0 (m, 10H). ^{19}F NMR (ppm): -80 (s, 3F), -173 (s, 1F). IR (CH_2Cl_2) (cm^{-1}): 3090 (C=C-H), 1380-1450 (C=N), 1270 (C-F). Mass spectral data; (m/e) calcd: 306.077990; found: 306.078043.

4-Fluoro-3,5-diphenylisoxazole (3e)

To 0.926 g (0.00410 mol) of compound 2a in 10 mL absolute EtOH was added 0.410 g (0.00590 mol) hydroxylamine hydrochloride. After 5 min, 2 mL concentrated sulfuric acid was added dropwise and stirred at room temperature for 20 h. The crude product was purified by chromatography and recrystallized from hexanes. 0.304 g (33%) of brownish crystals were obtained, m.p. 67-69°C. ^{1}H NMR (δ): 7-7.5 (m, 5H), 8-8.1 (m, 5H). ^{19}F NMR (ppm): -173 (s). IR (CCl_4) (cm^{-1}): 3060 (C=C-H), 1610 (C=N), 1200 (C-F). Mass spectral data; (m/e) calcd: 239.07872; found: 239.07845.

3-Anilino-2-fluoro-3-hydroxy-1,3-diphenylpropan-1-one (3f)

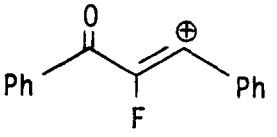
To 0.430 g (0.00178 mol) of compound 2a in 10 mL ethanol was added 0.163 mL (0.00178 mol) aniline. After 10 min, 0.0500 mL concentrated HCl was added dropwise and stirred for 36 h. 0.310 g (52%) of a yellowish solid was obtained upon filtration. ^{19}F NMR (ppm): -185 (d, J_{FH} = 50.1 Hz). ^{1}H NMR (δ): 3.7 (b. singlet, 1H), 5.25 (s, 1H, J_{HF} = 50.2 Hz), 6.5-7.0 (m, 5H), 7.15-7.5 (m, 10H). No mass spectra or melting point due to decomposition on column purification.

3-(3-Anisidino)-2-fluoro-3-hydroxy-1,3-diphenylpropan-1-one (3g)

To 0.985 g (0.00407 mol) of compound 2a was 10 mL glacial acetic acid was added 0.460 mL (0.00409 mol) m-anisidine. After stirring for 10 min, 2 mL of 0.0120 M HCl is added dropwise. Reaction mixture was stirred for 48 h. 0.860 g (58%) of a yellowish-brown solid was obtained. ^{19}F NMR (ppm): -186 (d, J_{FH} = 50.2 Hz). ^{1}H NMR (δ): 3.75 (1H, b. singlet), 5.2 (s, 3H), 5.5 (1H, d, J_{HF} = 50.2 Hz), 6.6 (m, 4H), 7.0-7.2 (m, 5H), 7.4-8.0 (m, 5H). Mass spectral data (m/e): 365. No melting point due to decomposition of product on column purification.

2-Fluoro-1,3-diphenylhex-2-en-1,5-dione (3h)

To 3.00 g (0.0124 mol) of compound 2a in 15 mL CH_2Cl_2 at -78°C was added 2.50 g (0.0124 mol) 2-(siloxyallyl)allane. Then, 1.53 mL (0.0124 mol) BF_3·Etherate was added dropwise. The mixture was allowed to warm to room temperature and stirred for 16 h. 0.959 g (27%) of a yellow solid was obtained, m.p. 173-175°C. ^{19}F NMR (ppm):

-140 (s). ^{1}H NMR (δ): 2.0 (s, 3H), 2.2 (s, 2H), 7.4-8.2 (m, 10H). Mass spectral data: no (m/e) = 282 was obtained due to decomposition of the product in GC column. A fragment with molecular weight of 225 (corresponding to ) was obtained as base peak.

SOURCES

1. (a) Filler, R.; Kobazasho, V. eds., Biomedical Aspects of Fluorine Chemistry, Kodansha, Tokyo, 1982. (b) Cohen, L.A.; Kirk, K.L. Biochemistry Involving Carbon-Fluorine Bonds, Am. Chem. Soc., Washington, DC, 1976.
2. Ishikawa, N. Bull. Chem. Soc. Jpn., 1981, 54, 3221.
3. Purrington, S. T.; Bumgardner, C. L.; Lazaridis, N. V.; Singh, P. J. Org. Chem., 1987, 52, 4307.
4. Machleidt, H.; Harimann, V. Justus Liebigs Ann. Chem. 1964, 679, 9.
5. Combes, C. Chem. Ber, 1896, 29, 2456. _____ C.R. Hebd. Seances Acad. Sci. Ser. C, 1887, 106, 142. _____ J. Prakt. Chem., 1896, 162, 340.
6. Streitweiser, A.; Heathcock, C. Introduction to Organic Chemistry, MacMillan Co., New York, 1976, Ch 35, Pp 1065-1112.
7. Bumgardner, C.L.; Whangbo, M.H. in Fluorine-Containing Molecules, ed. by J. Liebman, A. Greenberg, W.R. Dolbier; VCH Publishers, New York, 1988.
8. LInderman, R.J.; Kirollos, K.S. Tetrahedron Lett., 1989, Vol. 30, 16, 2049.
9. Meazza, G.; *et al.* Synthesis, 1990, 331.
10. Hosomi, A. J. Org. Chem., 1989, 54, 3254.
11. (a) Saunders, M.; *et al.* J. Am. Chem. Soc., 1973, 95, 3017. (b) Oligaruso, M.A.; *et al.* Chem. Rev.,1965, 65, 261.

12. Rekker, R.F., ed. Pharmacology of 1,3-Indandiones, Elsevier, New York, 1981.

13. Huheey, J.E., Inorganic Chemistry, Harper and Row, New York, 1978, p. 708.